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ASSESSMENT REPORT FOR MABTHERA

International non-proprietary name/Common name: rituximab

Procedure No. EMEA/H/C/165/II/0064

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Introduction

Mabthera contains the active substance rituximab which is a chimeric murine/human monoclonal antibody that binds CD20. CD20 is a hydrophobic transmembrane protein which is present on the cell surface of pre-B- and mature B-lymphocytes. In contrast the protein is considered absent on hematopoietic stem cells, pro–B–cells, normal plasma cells as well as other tissues.

CD20 is also present on malignant B-cells in most patients with mature B-cell lymphoma or B-cell leukemia. The binding of rituximab to CD20 on lymphocytes could lead to the elimination of these cells by means of several different mechanisms. The mechanisms include antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC) and apoptosis.

Mabthera was first authorised in 1998 in the European Union (EU/1/98/0067/002) and currently it is approved in the EU for the following indications:

- The treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

- The maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera.

- The treatment in monotherapy of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

- The treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

- MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

In 2008 the CHMP adopted a positive opinion on the indication for treatment of chronic lymphocytic leukemia (CLL):

- "MabThera is indicated for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy."

With the current procedure the MAH applies for extension of this indication in CLL via a type 2 variation. The proposed indication for CLL is "MabThera in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia."

2 Clinical aspects

2. 1 Clinical pharmacology

Pharmacokinetics

In study BO17072, in a subset of patients, pharmacokinetics of rituximab, fludarabine and cyclophosphamide was determined. It appears that there is no apparent effect of fludarabine and cyclophosphamide on the PK of rituximab and co-administration with rituximab did not appear to affect the PK of fludarabine or cyclophosphamide in CLL patients. However, it should be taken into account that for cyclophosphamide a high variability is observed in the pharmacokinetics which hampers a straight forward conclusion.

2. 2. Clinical studies

As stated the proposed indication for Mabthera is supported by the single pivotal study BO17072 and further by 8 additional phase II studies in which rituximab is combined with other chemotherapeutics. See table 1.

Table 1 Overview of the Content of the Submission Dossier

Study [Ref]	Title	Regimen	No of Patients Included	Source Document
Study BO17072	Phase III trial comparing FC to rituximab in combination with FC in previously treated patients with CLL	FC ± R	N=276 FC; N=276 R-FC	CSR
Wierda et al.	Chemoimmunoherapy with fludarabine, cyclophosphamide and rituximab for relapsed	R-FC	177 patients with recurrent/refractory CLL	Publication
Wierda et al.	and refractory chronic lymphocytic leukemia A retrospective comparison of three sequential groups of patients with recurrent/refractory chronic lymphocytic leukemia treated with fludarabine-based regimens	F, FC or R-FC	N=143 R-FC (out of 177 patients from above) N=251 F; N=111 FC	Publication
Hillmen et al.	NCRI CLL201 Trial: A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone with or without rituximab in previously treated CLL	FCM ± R	N=23 FCM; N=23 R-FCM	Conference abstract
Lamanna et al.	Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated CLL	R-PC	46 previously treated patients with CLL (n=32) or other low Grade B-cell neoplasms (n=14)	Publication
Lamanna et al.	Pentostatin, cyclophosphamide, rituximab, and mitoxantrone: A new highly active regimen for patients with CLL previously treated with PCR or FCR	R-PCM	21 previously treated patients with CLL (n=17) or other low Grade B-cell neoplasms (n=4)	Conference abstract
Robak et al.	Rituximab plus cladribine with or without cyclophosph. in patients with relapsed or	R-Cl± C	N=18 R-Cl; N=28 R-ClC	Publication

	refractory CLL			
Fischer et al.	Bendamustine in combination with rituximab for patients with relapsed CLL: A MC, phase II trial of the GCLLSG	R-B	81 patients	Conference abstract
Eichhorst et al.	CHOP plus rituximab in fludarabine refractory CLL or CLL with autoimmune hemolytic anemia or Richter's transformation: First interim analysis of a phase II trial of the German CLL Study Group	R-CHOP	34 patients refractory to F or with AIHA as well as in patients with Richter's transformation	Conference abstract
Keating et al	Salvage therapy following failure or relapse after FCR chemo-immunotherapy as initial treatment for chronic lymphocytic leukemia	Various, including R alone, R+HDMP, R+A and R-FC (+/- A or L)	79 patients with CLL relapsing after first-line R-FC	Conference abstract (and slides)
Total no. of relapsed/refractory CLL patients treated with rituximab			**741**	

Pivotal study (BO17072)

Methodology

Study BO17072 was an open-label, multicenter, 2 arm, 1:1 randomized, parallel group comparative, phase III study to evaluate the efficacy and safety of rituximab plus fludarabine and cyclophosphamide (R-FC) versus fludarabine and cyclophosphamide alone (FC) in previously treated patients with CD20 positive relapsed B-cell chronic lymphocytic leukemia (CLL). The choice of FC regimen as comparator is acceptable.

A pre-planned interim efficacy analysis of study BO17072 was performed with a clinical cut-off of June 26, 2007, after two-thirds (190/284 planned, 205 actual) of the events (progression or deaths) had been reported. But because the Independent Review Committee (IRC) assessed PFS did not cross the pre-specified threshold at that time (actual result: p=0.012) and because all patients had completed therapy, the DSMB recommended that the study should be continued until the final analysis. As a consequence, only results from the final analysis (data cut-off July 23 2008) are submitted.

The study was performed in 88 centers in 17 countries. The study design and the choice of dose chosen for study BO17072 was similar with regards to treatment regimens, response assessments and inclusion/exclusion criteria to the large, randomized phase III study in 817 patients with previously untreated CLL (ML17102) submitted to support the first line indication.
Patients were planned to receive 6 treatment cycles of FC chemotherapy (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] i.v. on days 1, 2 and 3 of each cycle) q28d. Patients randomized to the R-FC arm received FC in combination with rituximab (375 mg/m^2 i.v. on day 0 of cycle 1, 500 mg/m^2 i.v. on day 1 of cycles 2-6).

Main inclusion criteria

- Age ≥ 18 years
- Life expectancy > 6 months
- ECOG performance status 0-1
- B-CLL diagnosis according to the NCI criteria
- Previously treated with one of the following chemotherapy regimens:
    - single agent chlorambucil ± prednisone/prednisolone;
    - single agent fludarabine (or other nucleoside analogue);
    - alkylator-containing combination therapy (eg CHOP/CVP).
- ANC ≥ 1 × 10^9/L; Platelet count ≥ 50 × 10^9/L; Total bilirubin ≤ 2 × ULN; Alkaline phosphatase and transaminases ≤ 2 × ULN
- Creatinine clearance (Cockcroft and Gault) ≥ 60 mL/min
- Negative serum pregnancy test one week prior to treatment.

Main exclusion criteria

- Patients who had received prior combination treatment with cyclophosphamide and fludarabine either concurrently or sequentially.
- Patients who were refractory to fludarabine (or any nucleoside analogue). Refractory is defined as not achieving at least a PR for a minimum duration of 6 months.
- Patients who had had prior treatment with interferon, rituximab or another monoclonal antibody
- Prior allo or auto BMT/PSCT or eligibility for allo or autoBMT/
    - Clinically significant auto-immune cytopenia, Coombs-positive haemolytic anaemia
    - Prolonged use of glucocorticosteroids (> 1 month) for concomitant disease
    - Cumulative Illness Rating Scale score > 6
    - Transformation to aggressive B-cell malignancy
    - Active bacterial, viral or fungal infection
    - History of sever cardiac disease (CHF II or IV, recent myocardial infarction, unstable AP, entricular arrythmias.

Endpoints

Primary endpoint was progression-free survival (PFS). PFS is an acceptable primary endpoint in any CLL trial mainly because survival benefit is rarely observed in comparative clinical trials in this elderly population with a relatively indolent disease. Moreover, reduction in tumour burden often implies less constitutional symptoms and improvement in haemoglobin concentration, neutrophil and platelet counts.

Secondary endpoints were event free survival (EFS), disease free survival (DFS) in CR patients, duration of response (DR), overall response rate (CR, nPR, PR), overall survival (OS), proportion of patients with molecular remission. All secondary endpoints are conventional.

Statistical analysis

For the efficacy assessment a 2-sided, non-stratified Log-Rank test, Kaplan Meier curves, Cox regression analyses (adjusted and non-adjusted) were performed applying the Wald test. Response rates were compared using the Chi-squared test with 95% confidence limits according to Pearson-Clopper.

<u>Main characteristics of supportive studies</u>

To support the results of the pivotal trial, 8 phase II trials in relapsed/refractory patients with CLL were submitted. Overall, a total of 741 patients received rituximab in these studies. Approximately 460 patients were treated with rituximab in combination with various types chemotherapy i.e pentostatine, cladribine, fludarabine in combination with cyclophosphamide or bendamustine.

Since the proposed indication does not restrict combination chemotherapy to fludarabine and cyclophosphamide the studies can be considered as supportive in addition to BO17072.

2. 3. Results from Pivotal study (BO17072)

A total of 552 patients were enrolled and randomized (276 patients per arm). Six of these patients (4 patients FC, 2 patients R-FC) did not receive any study treatment. These patients were included in the intent-to-treat (ITT) population, but excluded from the safety analysis population (SAP).

Baseline characteristics.
Both treatment arms were well balanced with respect to disease stage and Eastern Cooperative Oncology Group (ECOG) status. At pre-therapeutic staging, 60% of patients had an ECOG performance status of 0, and 40% of patients had an ECOG performance status of 1. Slightly more patients in the FC arm than in the R-FC arm had B-symptoms at baseline (31% FC versus 26% R-FC). The median time from first diagnosis was nearly 4 years. Time from diagnosis was similar in the two treatment arms; FC median 3.7 years (range 0.1-23.4 years) and R-FC median 3.8 years (range 0.1-25.2 years).

Baseline hematology values were balanced between both treatment arms. Standard laboratory tests other than hematology parameters (β2-microglobulin, lactate dehydrogenase [LDH] and Coombs test) were balanced between the treatment arms at baseline.

The distribution of prognostic parameters and also cytogentic abnormalities was relatively balanced across the treatment arms.

In relation to characteristics regarding prior treatment it is not fully clear to what extent patients that were initially treated with fludarabine-based combination therapy (eg. FCR or FR) were to respond to re-treatment with these agents after relapse, retreatment appears a reasonable option. 17% of patients received prior fludarabine. Refractoriness to prior fludarabine may be of influence.

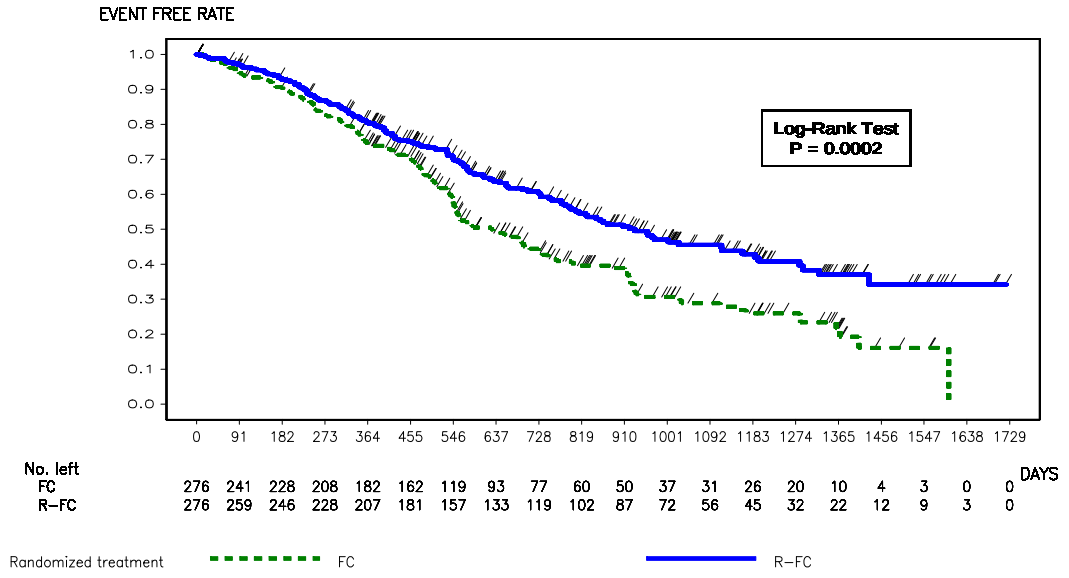
Patients' exposure to treatment
A total of 552 patients were enrolled and randomized in the study during July 2003-Augsut 2007.
Overall, the numbers of patients that withdrew from study treatment due to PD or patient refusal are relatively low (FC arm:38.6%, R-FC: arm 32.5%).

Efficacy Results

Primary endpoint progression free survival (PFS)
The primary efficacy analysis was based on a non-stratified, two-sided Log-Rank test of investigator assessed PFS. Progression-free survival was determined for the ITT population. At the time of the analysis (July 23, 2008), approximately 9% more patients in the FC arm than in the R-FC arm had experienced an event (progression or death; 158 patients [57%] on FC versus 132 patients [48%] on R-FC). More patients in the FC arm than in the R-FC arm had a progression as a first PFS event (48% FC versus 37% R-FC), whereas slightly more patients in the rituximab containing arm had died (9% FC versus 11% R-FC).

The addition of rituximab to the FC regimen significantly prolonged the median PFS when compared to the FC regimen alone (p=0.0002, Log-Rank test). The Kaplan-Meier estimated median PFS was 20.6 months (627 days) with FC and 30.6 months (932 days) with R-FC (see figure 1). The risk of having a PFS event (progression or death, whichever occurred first) was statistically significantly decreased by 35%: unadjusted HR = 0.65 (95% CI: 0.51, 0.82, p=0002, Wald test) for patients in the rituximab arm compared to the FC arm. 44% of the patients in the FC arm, and 60% of those in the R-FC arm, were progression-free at two years according to Kaplan-Meier estimates.

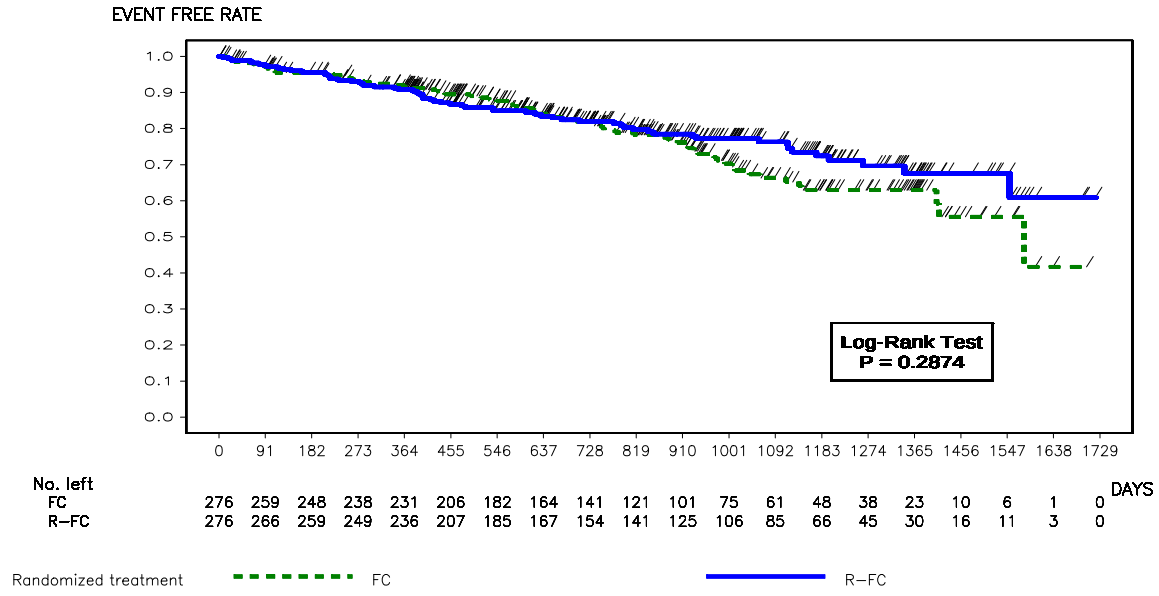
Figure 1 Kaplan-Meier Plot of Progression-Free Survival (BO17072 ITT population)



Overall survival (OS)

At the clinical cut-off (July 23, 2008) 130 randomized patients had died: 68 patients (25%) in the FC arm and 62 patients (23%) in the R-FC arm. The median survival time was (51.9 months) for patients in the FC arm and OS could not be estimated for patients in the R-FC arm. See figure 2.

Figure 2 Kaplan-Meier Plot of Overall Survival (BO17072 ITT)



Treatment with R-FC reduced the risk of death by 17% when compared to FC alone, however a difference which was not statistically significant (unadjusted HR 0.83; 95% CI: 0.59, 1.17; p = 0.2871, Wald test). At clinical cut-off, the data were still relatively immature, with the great majority of patients still alive in both treatment arms.

An overall survival analysis may be hampered by next line therapies. Besides that the study was not powered to demonstrate a benefit, any forthcoming assessment of survival in the study population, while excluding patients that subsequently received rituximab after failure of the 2nd line, is considered not an option. Very few randomised clinical studies including CLL patients have shown survival benefit reflecting a relatively long natural history in an elderly patient population. However, the

applicant has confirmed that overall survival data will continue to be collected and will submitted post approval.

Other secondary efficacy parameters.

Table 2 Summary of Best Overall Response (BO17072 ITT, investigator assessment)

	FC (N=276)		R-FC (N=276)
Responders$	160 (58.0 %)		193 (69.9 %)
Non-Responders	116 (42.0 %)		83 (30.1 %)
95% CI for Response Rates*	[51.9; 63.9]		[64.1; 75.3]
Difference in Response Rates		11.96	
95% CI for Difference in Response Rates#		[3.8; 20.1]	
p-Value (Chi-squared Test)		0.0034	
Odds Ratio		1.69	
95% CI for Odds Ratio		[1.19;2.40]	
Complete Response (CR)	36 (13.0 %)		67 (24.3 %)
95% CI for CR Rates*	[9.3; 17.6]		[19.3; 29.8]
Difference in CR Rates		11.23	
95% CI for Difference in CR Rates#		[4.6; 17.9]	
p-Value (Chi-squared Test)		0.0007	
Odds Ratio		2.14	
95% CI for Odds Ratio		[1.37;3.34]	
Partial Response (PR and nPR)	124 (44.9 %)		126 (45.7 %)
95% CI for PR and nPR Rates*	[39.0; 51.0]		[39.7; 51.7]
Difference in PR and nPR Rates		0.72	
95% CI for Difference in PR and nPR Rates#		[-7.8; 9.2]	
p-Value (Chi-squared Test)		0.8642	
Odds Ratio		1.03	
95% CI for Odds Ratio		[0.74;1.44]	
Stable Disease (SD)	61 (22.1 %)		47 (17.0 %)
95% CI for SD Rates*	[17.3; 27.5]		[12.8; 22.0]
Progressive Disease (PD)	15 (5.4 %)		7 (2.5 %)
95% CI for PD Rates*	[3.1; 8.8]		[1.0; 5.2]
Missing (not evaluable)	40 (14.5 %)		29 (10.5 %)

Value Of RSBOR But nPR Recoded To PR (RSBOR2)

BOR - best overall response based on investigator response assessment.
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of CR, PR or nPR

With the exception of DFS, the analysis of secondary endpoints are in line with the results on PFS for R-FC compared with FC as observed in the analysis of the key secondary efficacy parameters. The observation on DFS was also seen in the pivotal trial for the application for first line indication in CLL (study ML17102). Apart from DFS, results from other secondary endpoints can be considered supportive for the rituximab containing arm of BO17072.

Quality of Life (QoL)

QoL assessment, using the FACT-G questionnaire, up to one year after study onset, revealed no advantages for the addition of rituximab to FC. Nonetheless, although pivotal trial BO17072 was an open label study, any disadvantages with regard to rituximab appeared not to have affected QoL substantially.

Subgroup analysis of the pivotal study (BO17072)

In the study BO17072, in general the results of the PFS subgroup analyses were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the R-FC arm compared to the FC arm in almost all of the 48 subgroups analyzed.

Only the subgroup of patients who received treatment ≥ 10 years from first diagnosis (unadjusted HR = 1.02; 95% CI: 0.52, 1.99), and the subgroup of patients with negative CD38 at baseline (unadjusted HR = 1.04; 95% CI: 0.67, 1.64) had a hazard ratio >1.0.

In all other subgroups, the risk of disease progression or death was reduced with a risk reduction ranging from 1% (for patients > 70 years old) to 80% (for patients who were ZAP70+ and had mutated IgVH). In most of the subgroups analyzed, the risk reduction ranged between 40% and 60% and point estimates (not adjusted) were below 1 indicating a clinical benefit for R-FC.

The risk of progression or death was reduced in patients with and without del17p (del17p being a poor prognostic marker and associated with treatment resistance) and in all Binet stages. Subgroup analyses for OS, based on baseline prognostic parameters and putative prognostic markers, were consistent with the results of OS in the overall population and with the PFS analysis. Although subgroups were small and relatively few events were observed, there was a tendency towards a reduced risk of death with R-FC compared to FC for most of the subgroups analyzed.

2. 4. Supportive studies: efficacy

Patient populations in the supportive studies

In the supportive studies of rituximab in combination with chemotherapy in patients with previously treated CLL, the median age was in the range of 59 to 66 years. Patients enrolled in the supportive studies were slightly younger than the median age of diagnosis for CLL (65-72) but similar to patients in the pivotal study BO17072. Apart from the study by Wierda et al. (in which half of the patients had Rai stage 0-2 disease), the majority of patients enrolled in the supportive studies had high risk disease (between 59% and 86% of patients had Rai stage ≥ 3 disease or approximately two-thirds of patients with Binet stage C disease), and treatment had failed after a median of two prior therapies for CLL.

Progression free survival (PFS)

Results of PFS were available from 2 studies in previously treated patients with CLL (see table 3).

- One retrospective cohort analysis comparing fludarabine alone with fludarabine/cyclophosphamide, and rituximab in combination with fludarabine and cyclophosphamide (refer to Wierda et al. See table 1).
- One study investigating the combination of rituximab and cladribine with or without cyclophosphamide (refer to Robak et al.).

Table 3 Overview of Progression-free Survival Across Studies in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Study	**BO17072**		**Wierda et al.[#]**			**Robak et al.**
	FC N=276	**R-FC N=276**	**F N=251**	**FC N=111**	**R-FC N=143**	**R-Cl± C N=46**
Median FU	25.3 mo		19 mo	29 mo	34 mo	16 mo
Median PFS (95% CI)	20.6 mo (18.1, 24.0)	30.6 mo (26.1, 38.2)	26 mo	36 mo	32 mo	12 mo (range 4-46)
p-value (Log Rank test)	0.0002		< 0.01		ns	na

[#] Results reported for patients with PR and CR only (59% of patients treated with F, 67% of patients treated with FC, 72% of patients treated with R-FC)

* measured from the time of first response to the time of documented disease relapse, progression or death

** including patients with PLL, MCL and Richter transformation Abbreviations: mo, months; ns not significant; na, not available; FU, follow up.

Overall Survival
In the retrospective comparison of three sequential groups of patients with relapsed/refractory CLL (refer to the paper by Wierda et al.), estimated median survival times were significantly longer for patients in the R-FC cohort compared to patients in the FC or F cohort ($p = 0.05$ for R-FC vs FC and $p<0.01$ for R-FC vs F). Median OS was 49 months (R-FC), 31 months (FC) and 19 months (F), respectively. Note that OS results in non-randomized comparisons should be interpreted with caution.

In a small study including 34 poor prognostic patients with relapsed/refractory CLL (refer to Lamann et al. See table 1), the median survival was 44 months for patients treated with rituximab in combination with PC.
In a retrospective review of patients receiving a range of salvage therapies after failure of first-line R-FC therapy, the median survival after first salvage therapy was 30 months and was significantly longer for patients who achieved a CR or nPR with first salvage therapy (median 46 months) than for those who only achieved a PR or no response (median 10 months). Duration of response to first-line R-FC, β2-microglobulin level and Rai stage predicted survival after salvage therapy but the actual salvage regimen did not (refer to the Mabthera registration study on 1st line CLL, ML17102).

Overall Response rates
In supportive studies, ORRs were similarly high and ranged from 67% (rituximab in combination with cladribine) to 94% (rituximab in combination with PCM). In the retrospective analysis by Wierda et al. (Cancer, 2006, 106:37-345), the overall response rate was significantly higher for patients who had received R-FC compared with patients who had received fludarabine ($p=0.008$), but not compared to patients who received FC. However, the proportion of CRs was significantly higher in patients in the R-FC cohort compared to patients in the fludarabine and FC cohorts ($p<0.05$).

2. 5. Clinical safety

Introduction
The safety population (SAP) in study BO17072 consisted of 546 patients (272 patients on FC, 274 patients on R-FC). An overview of the safety data reported in this study with a clinical cut-off date of July 23, 2008 is shown in Table 4.

Table 4 Overview of Adverse Event Experience (SAP)

	FC N = 272 No. of patients (%)	**R-FC N = 274 No. of patients (%)**
Any adverse events	260 (96%)	270 (99%)
Grade 3/4 AEs	200 (74%)	219 (80%)
Serious Adverse Events	130 (48%)	137 (50%)
Fatal AEs	26 (10%)	36 (13%)
AE leading to dose modification/interruption	105 (39%)	141 (51%)
AE leading to treatment discontinuation	69 (25%)	72 (26%)
Total deaths	68 (25%)	62 (23%)
Treatment-related deaths	14 (5%)	19 (7%)

Overall, the safety profile of rituximab in CLL was consistent with its expected safety profile and no unexpected new safety signals were detected. There were more cases of hepatitis B (primary infection and reactivation) than expected in the R-FC arm, a slight imbalance in second malignancies compared with the FC arm.

Adverse events
Overall, patients in the R-FC arm experienced more AEs than patients in the FC arm (1468 AEs in FC, 1797 AEs in R-FC), mostly due to AEs in the following system organ classes (SOCs):

Table 5 Adverse events

Vascular disorders:	4% and 17% in the FC arm and R-FC arm
Respiratory, thoracic and mediastinal disorders :	21% and 28%
Skin and subcutaneous tissue disorders:	25% and 31%
Metabolism and nutrition disorders:	9% and 15%
General disorders:	46% and 54%
Musculoskeletal and connective tissue disorders:	18% and 22%
Gastrointestinal disorders:	55% and 58%
Blood and lymphatic system disorders:	67% and 70%
Ear and labyrinth disorders	<1% and 3%

All Grade AEs which occurred with an at least 2% higher incidence in the R-FC arm than in the FC arm are summarized in Table 5. Overall, the slightly higher frequencies and the types of events (all Grades) observed in the R-FC arm are consistent with the known safety profile of rituximab and do not pose any new safety concerns.

Grade 3/4 AEs which occurred with a 2% or higher incidence in the R-FC arm compared with the FC arm are summarized in table 6, and include (febrile) neutropenia, granulocytopenia and hepatitis B infections. This information is used to update the prescribing information.

Table 6: Summary of Grade 3/4 Adverse Events with ≥ 2% Higher Incidence in the R-FC Arm Compared to the FC Arm (SAP)

Body System/ Adverse Event	FC N=272 No. (%)	R-FC N=274 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	108 (39.7)	116 (42.3)
FEBRILE NEUTROPENIA	32 (11.8)	40 (14.6)
GRANULOCYTOPENIA	12 (4.4)	18 (6.6)
INFECTIONS AND INFESTATIONS		
HEPATITIS B	-	6 (2.2)

Multiple occurrences of the same adverse event in one individual counted only once.
Only AEs with a missing onset date or an onset date on or after the date of first trial medication are considered.

Neutropenia and febrile neutropenia are already reported in the prescribing information with the same frequency grouping “very common” (incidence of ≥ 10%). Granulocytopenia has not been reported in the prescribing information and it is proposed to report it in the “common” frequency grouping (≥ 1% <10%).

The incidence of thrombocytopenia in the R-FC arm of study BO17072 was slightly higher (1.8%) than in the FC arm but this is not captured in table 5 which uses a 2% cut-off. This event is already reported in the prescribing information in the frequency grouping “common” and, based on the frequency observed in study BO17072, the MAH proposes that this be changed to “very common”.

Based on the incidence of hepatitis B cases observed in study BO17072 (6 patients with a Grade 3/4 event with 5 patients actually experienced Grade 3/4 hepatitis B the MAH proposes to report this event in the “common” frequency grouping and to update the Warning Section in the prescribing information.

The proportion of Grade 3/4 AEs considered by the investigators to be related (remotely, possibly or probably related) to treatment was slightly higher in the R-FC arm (83% of Grade 3/4 AEs in the FC arm vs. 86% of Grade 3/4 AEs in the R-FC arm) and the proportion of patients with a Grade 3/4 related AE was higher in the R-FC arm (67% FC vs. 74% R-FC).

More patients in the R-FC arm had a grade 3/4 related AE within the blood and lymphatic system disorders SOC (59% of patients in the FC arm vs. 64% of patients in the R-FC arm) and within the infections and infestations SOC (16% FC vs. 14% R-FC).

The incidence of grade 3 and 4 infections (mainly pneumonia, herpes zoster, sepsis or bronchitis) was comparable between the treatment groups. There was no consistent increase in infection rates across different age categories or disease stages according to Binet. A total of 31 patients died from infections, 19 patients (5%) in the FC arm and 12 patients (3%) in the R-FC arm. In 5 patients in the FC arm and in 4 patients in the R-FC arm, death due to infection was considered treatment-related.

Overall, with the exception of hepatitis B, the slightly higher frequencies and the types of Grade 3/4 adverse events observed in the R-FC arm are consistent with the known safety profile of rituximab and do not pose any new safety concerns.

Deaths and Serious adverse events

Deaths
General disorders and administration site conditions, including progressive disease (PD), were the major cause of death in both treatment arms (18 patients (7%) in FC vs. 17 patients (6%) in R-FC). Infections and infestations (including pneumonia, septic shock and sepsis) were responsible for the deaths of 19 patients (7%) in the FC arm and 14 patients (5%) in the R-FC arm. Fourteen patients died due to cardiac disorders (6 patients (2%) in FC, 8 patients (3%) in R-FC).
The investigators considered 14 deaths (5%) in the FC arm and 19 deaths (7%; including one death due to Stevens-Johnson syndrome [probably related to cefotaxime] and one death from Hodgkin's disease/CLL transformation) in the R-FC arm related to treatment.
Of the 33 patients who died from infections and infestations, 16 deaths were considered to be related to study treatment (3% [7/272] in FC vs. 3% [9/274] in R-FC).

SAEs
A slightly higher incidence of SAEs was observed in the R-FC arm (130 patients [48%] in FC; 137 patients [50%] in R-FC with at least one serious adverse event [SAE]).
A slight increase in incidence of febrile neutropenia was observed in the R-FC arm (11%) compared to the FC arm (8%), while there was a higher incidence of anemia (reported as an SAE) in the FC arm (4% in FC vs 1% in R-FC). An equal number of patients in each arm (54 patients [20%]) experienced an SAE categorized under infections and infestations, although SAEs of hepatitis B infection occurred only in the R-FC arm (6 patients). 36% of the patients in the FC arm experienced at least one treatment-related SAE compared to 39% of patients in the R-FC arm.

Secondary malignancies
Overall, 40 patients experienced 44 AEs classified as neoplasm (17/272 [6%] in FC; 23/274 [8%] in R-FC). Furthermore, 36 patients experienced SAEs classified as neoplasm (15 patients in FC and 21 patients in R-FC) and 12 patients had fatal AEs classified as neoplasm (2 patients in FC [3 events] and 10 patients [11 events] in R-FC).

Laboratory findings
A higher number of shifts to Grade 3/4 values in the R-FC arm were observed for white blood cells, lymphocytes and neutrophils compared to the FC arm, which correlated with the increased incidence of neutropenia, febrile neutropenia and granulocytopenia. Higher frequency of shifts to Grade 3/4 levels was observed in the R-FC arm for AST, ALT, total bilirubin and to lesser extent LDH. The reason for this imbalance between the arms is not clear. There was no corresponding imbalance between the FC and R-FC arms for hepatobiliary AEs, Grade 3/4 AEs or SAEs, with the exception of hepatitis B. The cases of acute or chronic hepatitis B infection and/or reactivation in the R-FC arm may account for some of the difference in Grade 3/4 liver function test abnormalities between the two arms but, these do not fully account for the difference as observed.

Supportive studies: safety
The safety data on rituximab in combination with chemotherapy in the supporting studies is consistent with the safety profile in the pivotal study, BO17072. In particular, myelotoxicity and gastrointestinal disorders were seen in both the pivotal and the supportive trials and related to the use of rituximab.

Risk Management plan

The MAH has submitted an updated combined Risk Management Plan (RMP) for rituximab in the indications rheumatoid arthritis (RA), non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL), version 3.1. The applicant announced that the only significant new data included in the updated RMP are in the oncology sections: data on rituximab in the treatment of patients with relapsed/refractory CLL became available from study BO17072 (REACH). Also, new data are included in the paediatric off-label section; however, these changes do not present new safety findings.

Table 7 Summary of the EU Risk Management Plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
RA – Identified Risks		
(Serious) Infections	Routine + Pharmacoepidemiology studies*	*Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active and/or severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3) or severely immunocompromised patients (e.g. in hypogammaglobulinemia or where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).* *Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.* *Very rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported following use of MabThera for the treatment of rheumatoid arthritis and autoimmune diseases including Systemic Lupus Erythematosus (SLE) and Vasculitis. These cases involved patients with multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy.* *In patients with non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, very rare cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma).*
RA – Identified Risks		
Acute Infusion-Related Reactions	Routine + Pharmacoepidemiology studies*	As described in sections 4.2 and 4.4 of the SmPC: ***4.2 Posology and method of administration*** *Method of Administration* *Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.* *Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered bedore each infusion of MabThera.* *First infusion* *The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.* *Subsequent infusions*

		Subsequent doses of MabThera can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr. *The prepared MabThera solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.*
		4.4 Special warnings and precautions for use '*Infusion reactions* *MabThera is associated with infusion reactions, which may be related to release of cytokines and/or other chemical mediators. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of these events (see section 4.8).* *Most infusion events reported were mild to moderate in severity. The proportion of affected patients decreases with subsequent infusions. The reactions reported were usually reversible with a reduction in rate, or interruption, of MabThera infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. In most cases, the infusion can be resumed at a 50 % reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.* *Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins, including MabThera, to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. The presence of HACA may be associated with worsening infusion or allergic reactions after the second infusion of subsequent courses (see section 5.1).* *In clinical studies 10/990 (1 %) patients with rheumatoid arthritis who received a first infusion of MabThera at any dose experienced a serious reaction during the infusion (see section 4.8).*

Impaired immunization Response	Routine + Pharmacoepidemiology studies*	As described in section 4.4 of the SmPC: *4.4 Special warnings and precautions for use* *Immunization* *Physicians should review the patient's vaccination status and follow current immunization guidelines prior to MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.* *The safety of immunization with live viral vaccines following MabThera therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on MabThera or whilst peripherally B cell depleted.* *Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomized study, patients with RA treated with MabThera and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs. 93%), when given 6 months after MabThera as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera.* *In the overall experience of MabThera repeat treatment over one year, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.*
RA – Potential Risks		
Infections (including serious viral infections, opportunistic infections and PML)	Routine + Pharmacoepidemiology studies* The occurrence of PML will be monitored through the sponsor's routine pharmacovigilance system. For events reported to the sponsor's pharmacovigilance system as spontaneous reports, additional data will be collected by means of a Guided Questionnaire.	See recommendations for (Serious) infections above
Malignancies	Routine + Pharmacoepidemiology studies*	As described in section 4.4 of the SmPC: ***4.4 Special warnings and precautions for use*** *Malignancy* *Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients (see section 4.8) a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.*

Pregnancy/lactation	Routine + Pharmacoepidemiology studies*	As described in section 4.6 of the SmPC: ***4.6 Pregnancy and lactation*** *<u>Pregnancy</u>* *IgG immunoglobulins are known to cross the placental barrier.* *B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.* *Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy.* *Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase.* *<u>Lactation</u>* *Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.*
Impact on cardiovascular disease	Routine + Pharmacoepidemiology studies*	~~Routine: The SmPC currently advises the following;~~ As described in section 4.4 of the SmPC: ***4.4 Special warnings and precautions for use*** *"There are no data on the safety of MabThera in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MabThera, the occurrence of pre-existing ischemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MabThera and patients closely monitored during administration. Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medications 12h prior to the MabThera infusion"*
Gastrointestinal perforation	Routine + Pharmacoepidemiology studies*	Routine: GI perforations in patients treated in autoimmune indications will continue to be monitored by the MAH.
RA – Missing Information		
Immunogenicity and autoimmune disease	Routine	N/A

Acute infusion related reactions	Routine	As described in section 4.2 and 4.4 of the SmPC: ***4.2 Posology and method of administration*** *Method of Administration* *Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.* *Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered bedore each infusion of MabThera.* *First infusion* *The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.* *Subsequent infusions* *Subsequent doses of MabThera can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.* *The prepared MabThera solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus.* ***4.4 Special warnings and precautions for use*** *Patients with a high tumour burden or with a high number (≥25 x 10^9/l) of circulating malignant cells such as patients with CLL , who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocytes count is still > 25 x 10^9/L….*
		Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have been resolved or ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome. *Infusion related adverse reactions including cytokine release syndrome (see section 4.8) accompanied by hypotension and bronchospasm have been observed in 10 % of patients treated with MabThera. These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen,*

		intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions. *Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticooids, should be available for immediate use in the event of an allergic reaction during administration of MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.*
Infections	Routine	As described in section 4.4 of the SmPC: ***4.4 Special warnings and precautions for use*** *Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active severe infection (eg. tuberculosis, sepsis and opportunistic infections, see section 4.3).* *Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).*
Neutropenia	Routine + planned analysis of prolonged neutropenia in ML17102/CLL-8 study	As described in section 4.4 of the SmPC ***4.4 Special warnings and precautions for use*** *Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy, regular full blood counts should be performed according to usual medical practice.*
HBV reactivation	Routine	As described in section 4.4 of the SmPC: ***4.4 Special warnings and precautions for use*** *Cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome The majority of these subjects were also exposed to cytotoxic chemotherapy. Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy. Hepatitis B virus (HBV) screening should be considered for high risk patients before initiation of treatment with MabThera. Carriers of hepatitis B and patients with history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during and for several months following MabThera therapy.*

NHL/CLL – Identified Risks (continued)		
Tumor lysis syndrome	Routine	See Acute infusion related reactions recommendations above. *Maintenance of adequate hydration and urine output are crucial in preventing TLS. Allopurinol and/or rasburicase are also recommended depending on the risk group. Patients at low-risk of TLS may require no additional treatment other than hydration. Those with intermediate risk require allopurinol with the addition of rasburicase if hyperuricaemia still develops. Vigorous hydration is recommended for all patients in the middle-to-high risk groups and for those with diagnosed TLS. Rasburicase is recommended for patients with hyperuricaemia associated with a diagnosis of TLS or in the initial management of high risk paediatric patients.*
PML	Routine + continued expedited reporting of new cases/guided questionnaire used to better characterise all such reports (all indications).	Please refer to section 4.4 of the SmPC ***4.4 Special warnings and precautions for use*** *Progressive Multifocal Leukoencephalopathy* *Use of MabThera maybe associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a Neurologist should be considered as clinically indicated.* *If any doubt exists, further evaluation, including MRI scan preferably with contrast, CSF testing for JC Viral DNA and repeat neurological assessments, should be considered.* *The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.* *If a patient develops PML the dosing of MabThera must be permanently discontinued.* *Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.*

Serious viral infection	Routine	See Infections recommendations above
GI perforation	Routine	There are no known ways of preventing GI perforation in patients receiving rituximab for hematological malignancies.
Impaired immunization response	Routine	As described in section 4.4 of the SmPC. ***4.4 Special warnings and precautions for use*** *The safety of immunization with live viral vaccines, following MabThera therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations. However with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received MabThera monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.* *Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera.*
NHL/CLL – Potential Risks		
Prolonged B-cell depletion	Routine + results of PRIMA (MO18264) study (expected 2010 or 2011) Results of ML19514 and ML18434 (expected after December 2010)	B-Cell depletion is the expected therapeutic outcome with rituximab. Prolonged B-cell depletion/delayed B-cell recovery is currently not listed as a potential risk in the rituximab SmPC but detailed information on B-cell and immunoglobulin changes is provided.

Grade 3/4 and serious blood and lymphatic AEs in patients > 70 years with CLL	Routine	Routine. The SmPC already includes information on blood and bone marrow system disorders (without reference to age categories). The following new text is also proposed for the SmPC in Section 4.4.): ***4.4* Special warnings and precautions for use** Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/l and/or platelet counts < 75 x 10^9/l as clinical experience in this population is limited. MabThera has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity. Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy, regular full blood counts should be performed according to usual medical practice. The following new text is also proposed for the SmPC *Elderly patients (≥ 65 years)* The incidence of Grade 3/4 blood and lymphatic adverse events was higher in elderly patients (≥ 65 years of age) compared to younger patients, with previously untreated or relapsed/refractory CLL.
Opportunistic infections	Routine	~~Routine: See Infections~~ See recommendations for infections above
AML/MDS	Routine	Routine: There are no known ways of reducing the risk of treatment-related secondary AML/MDS, other than by reducing exposure to chemotherapy and radiotherapy and/or by substituting a less DNA-damaging agent, if possible (eg, substitution of ABVD for MOPP chemotherapy in Hodgkin's lymphoma **[8732]**).
Second malignancies	Routine, guided questionnaire + further results of REACH (BO17072) expected in Q4 2010	N/A
NHL/CLL – Missing Information		
Prolonged neutropenia	See neutropenia above	See neutropenia above

*Pharmacoepidemiology studies refer to the Registry studies (British Society of Rheumatology Biologics Register (BSRBR) and the AntiRheumatic Therapy in Sweden Group (ARTIS) discussed in Section 1.2.1.6 (Epidemiology studies) and in Section 3.3.1 in the respective pharmacovigilance plans). The BSRBR prospectively evaluates the safety profile of biologic agents, in particular the risks of neoplasms, serious co-morbidity and death in cohorts of patients taking particular biologics, compared with a cohort of patients who are being treated with non-biologic DMARDS only. The Swedish Registry is performing a post-marketing surveillance study including the presently available biologics used in treating patients with rheumatic diseases. This is performed in collaboration with the Swedish Society of Rheumatology and the Swedish Medical Products Agency, and aims to provide long term safety data on major comorbidities with the use of biologics.

3. Overall Discussion and Benefit/ Risk Assessment

The proposed indication for rituximab in combination with chemotherapy in patients with relapsed/refractory CLL is based on data from one pivotal study (BO17072 -REACH). This was a multicentre/multinational, open label, prospectively planned, randomised controlled study. In this study 552 patients were randomly assigned to treatment groups through a central randomisation to either the combination of R-FC or FC alone. In view of current practices in this patient group the choice of the treatment modalities and schedules in the active and the control arms are considered justified.

Although a pre-planned interim efficacy analysis of study BO17072 was performed after two-thirds (190/284 planned, 205 actual) of the events (progression or deaths) had been reported, it was decided that PFS did not cross the pre-specified threshold at that time (actual result: p=0.012) and, because all patients had completed therapy, the data monitoring board recommended that the study should be continued until the final analysis. As a consequence, only results from the final analysis (data cut-off July 23 2008) were submitted.

The primary endpoint was the Progression-free Survival (PFS); the secondary endpoints included the Event-free Survival, Overall Survival (OS), Disease-free Survival (DFS), Overall Response Rate and Time to new CLL Treatment. Although in general PFS is considered a surrogate endpoint when assessing efficacy, in the setting of 2nd line treatment of CLL this endpoint can nevertheless be considered of clinical relevance especially when assessment of OS may be hampered by the effect of next line therapies.

The patient population studied can be considered as representative for the general population with relapse or refractory CLL and baseline characteristics appeared balanced between the two treatment arms. Patients with ECOG PS >1 were not eligible.

Results from BO17072 on PFS showed substantial improvement of PFS: The KM estimate in the ITT population showed median PFS of 20.6 months with FC versus 30.6 months with R-FC. This difference is statistically significant (p=0.0002) and the HR was 0.65 (95% CI 0.51 - 0.82). Therefore this pivotal trial BO17072 data on PFS showed a statistically significant and clinically relevant improvement of the Progression free Survival. In addition, an increase in Event-free Survival and Overall Response Rate confirmed the benefit for rituximab plus FC in patients with relapsed or refractory CLL. Although a trend towards an OS benefit is envisaged, formal proof of benefit in survival is lacking possibly due to next line treatments and also QoL improvement was not demonstrated.

The treatment benefits observed with R-FC were seen in nearly all of the subgroups analyzed except for patients that relapsed >10 years after initial treatment and for patients with CD38 negative CLL phenotype (a prognostic favourable subgroup).
From the supportive studies it may be concluded that the addition of rituximab to various appropriate other chemotherapy regimens for relapsed CLL improves efficacy regarding PFS, although also here, as in trial BO17072, indications of survival benefit are limited.

With regard to safety, the risks of rituximab in CLL patients were comparable to known safety profiles of rituximab used in approved indications in combination with other cytotoxic chemotherapy regimens. In particular, higher incidences of neutropenia, leukopenia, febrile neutropenia and pancytopenia were also seen in patients treated with rituximab for 1st line treatment of CLL and in NHL. The addition of rituximab did not increase the rate of treatment discontinuations due to toxicity or the incidence of treatment related deaths compared to FC alone.
Myelotoxicity, hepatitis B and secondary neoplasms were more apparent in the R-FC arm.

Overall, the benefits of the addition of rituximab to the combination fludarabine and cyclophosphamide with regard to PFS outweigh the risk related to this addition. The PFS benefit in relapsed or refractory CLL is substantial, 10 months, and this clearly reflects a clinically relevant

advantage. Although OS benefit could not be proven, it can be envisaged that rituximab leads to prolonged survival as well. Therefore the benefit/risk ratio is considered positive.
The application could be approvable, provided other concerns are resolved.

The indication for first line treatment of chronic lymphocytic leukemia (CLL) was recently approved. Consequently, it can be foreseen that in future patients, that may encounter refractoriness to 1st line treatment, or patients that may relapse after initial treatment, will have had rituximab as part of prior first line therapy.

Study BO17072 excluded patients who were previously treated with rituximab or other monoclonal antibodies. At the time of study planning in 2001 and 2002, patients who had received monoclonal antibody treatment in the first-line setting were considered rare as no monoclonal antibodies were approved for the first-line treatment of patients with CLL. Standard first-line treatments were mainly fludarabine monotherapy and chlorambucil (with or without corticosteroids), the two first-line regimens that contributed most to the patient pool in study BO17072 (REACH).

During the last 5-7 years, use of first-line fludarabine and cyclophosphamide (FC) combinations has increased as a result of a number of randomised phase III trials showing superiority of fludarabine over chlorambucil, and of FC over fludarabine monotherapy. Meanwhile, the ML17102 (CLL-8) trial has demonstrated that the addition of rituximab to FC (R-FC) is superior to FC alone, with higher response rates and complete response (CR) rates, and longer progression-free survival (PFS) reported. Accordingly, it is expected that R-FC will rapidly become the combination of choice for patients with previously untreated CLL who are suitable for fludarabine-based therapy. However, the ML17102 (CLL-8) study data also indicate that although patients treated with R-FC benefit from the prolongation of PFS, ultimately most patients will still relapse and require further therapy.

Limited data that are available from approximately 180 patients demonstrate that rituximab-containing regimens, specifically repeat administration of R-FC (and variants thereof) are a viable and useful therapeutic option for patients whose initial treatment contained rituximab. There is no data published indicating that regimens that do not contain rituximab produce better outcomes than regimens that do incorporate rituximab. An exclusion of CLL patients who have previously received rituximab-containing therapy from treatment with rituximab-containing combinations at relapse would limit the available options therefore it was considered appropriate to leave the treatment decision to the clinician.

The overall results of salvage therapy after first-line FCR therapy are unsatisfactory as stated by Keating et al. That fact may be due both to refractoriness to the two most important classes of cytotoxics for CLL, *alkylating agents* (cyclophosphamide) and *fluoropyrimidines* (fludarabine), and to *anti-CD20* therapy (rituximab). It seems much more likely that refractoriness to conventional chemotherapy plays a major role in the unsatisfactory second-line response than the limited contribution of rituximab. Therefore, a restrictive wording as regards rituximab is not justified. However, it seems that the results from study BO17072 may not be fully translated to that particular population of CLL patients. If FCR becomes standard first line therapy for CLL patients who can tolerate this regimen the same regimen may not be generally appropriate as second-line therapy. The decision to use FCR as second-line therapy in that population may depend on a number of other factors (primary refractoriness to FCR, early relapse after initial FCR, long disease-free interval after FCR, patient tolerability and performance status etc.). Such clinical decisions are not easily transferable to the SPC wording, hence the following statement was agreed: “Limited data on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to fludarabine or any nucleoside analogue are available.”

Rituximab is currently not licensed in paediatric NHL. The MAH is working with paediatric collaborative groups to support a randomised international clinical trial in which about 300 paediatric patients will be treated with rituximab (plus 300 controls), and in which all adverse events will be collected up to 5 years. In addition, the MAH is planning to implement an enhanced pharmacovigilance system in August 2009, which will proactively follow up all paediatric adverse event reports received by the MAH, including reports of ‘off-label’ use. This will utilise a ‘guided

questionnaire' to better characterise the reports. The guided questionnaires will be 'tracked' and followed up closely. This information will be included in the periodic safety update report (PSUR) which is submitted to the EMEA on a regular basis.
Both these proposals have been described in the rituximab Paediatric Investigation Plan.

The MAH confirmed that collection of overall survival data will continue. The MAH intends to submit one updated analysis on overall survival with a clinical data cut-off approximately 24 months after the cut-off for the final analysis (data cut-off for final analysis was July 23, 2008). The up-dated OS data will be submitted to the EMEA about 5 months later, ie around Dec 2010. It is expected that with this additional follow-up, about 40-50% of deaths will have been observed in the BO17072 (REACH) study. Further follow-up for survival is not planned after the 2010 cut-off, since results of the primary analysis of the study were released to the public in November 2008 and substantial cross over to rituximab is expected to occur which will confound any future analyses. Accordingly, it is considered unlikely that an OS benefit will be observed at the next OS update or subsequently.

Benefits
Superior efficacy for the primary endpoint PFS has been convincingly demonstrated in favour of the rituximab containing combination. The primary endpoint of PFS was prolonged by a median of 10 months (20.6 months for FC and 30.6 months for R-FC) and the risk of disease progression or death was reduced by 35% when rituximab was added to the FC regimen (p=0.0002, Log-Rank test). This PFS benefit was robust and apparent in almost all of 48 pre-specified subgroups.

In addition, an increase in Event-free Survival and Overall Response Rate confirmed the benefit for rituximab plus FC in patients with relapsed or refractory CLL. Also a trend towards an OS benefit is envisaged, but as the overall survival data may be hampered by subsequent treatment options, the data may be difficult to interpret.
From the supportive studies it may be concluded that the addition of rituximab to various appropriate other chemotherapy regimens for relapsed CLL improves efficacy regarding PFS, although also here indications of survival benefit are limited.

Risks
With regard to safety, the risks of rituximab in CLL patients were comparable to the well known safety profile of rituximab. The safety profile of rituximab plus FC was very acceptable with only the expected addition of rituximab-related side effects to those of FC (more infections and more infusion-related events).
The patient numbers included in the analysis might have been too small to detect prognostic factors for secondary malignancies. Inclusion of "second malignancies" as a potential risk for NHL and CLL in the RMP is accepted. Routine pharmacovigilance activities including discussion and monitoring of second malignancies from spontaneous reporting and other sources in PSURs is considered sufficient at this moment. For each case report of second malignancy the MAH should analyse and report whether a causal relationship between the event and rituximab can be excluded. The overall discussion of second malignancies should always be based on cumulative data from all sources (all reports up to the data lock point). The MAH commits to provide the relevant information as asked for in the next and following PSURs.

Balance
Overall, the benefits of the addition of rituximab to the combination fludarabine and cyclophosphamide with regard to PFS outweigh the risk related to this addition. The PFS benefit in relapsed or refractory CLL is substantial, 10 months, and this clearly reflects a clinically relevant advantage. Although OS benefit could not be proven, it can be envisaged that rituximab leads to prolonged survival as well.
The benefit/risk ratio is considered positive, as the MAH revised the SPC according to the CHMP recommendations provided and committed to provide follow-up information.

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.